



NTP
National Toxicology Program

Report on the NTP Technical Reports Peer Review Panel Meeting February 8-9, 2012

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Draft Technical Reports Peer Reviewed on February 8-9

- *N,N*-Dimethyl-*p*-toluidine
- *Ginkgo biloba* Extract
- β -Picoline
- Pyrogallol
- Trimethylolpropane Triacrylate
- 3' -Azido-3' -deoxythymidine (AZT)
- 3' -Azido-3' -deoxythymidine (AZT) in combination with Lamivudine (3TC) and Nevirapine (NVP)

Technical Reports Peer Review Panel Roster

Stephen Roberts, PhD, University of Florida (Panel Chair)

Jane Alcorn, DVM, PhD, University of Saskatchewan

Lucy Anderson, PhD, DABT, Private Consultant

Hillary Carpenter III, PhD, Minnesota Department of Health

Russell Cattley, VMD, PhD, DACVP, Auburn University

Michael Elwell, DVM, PhD, Covance Laboratories, Inc.

Jon Mirsalis, PhD, DABT, SRI International

Ofelia Olivero, PhD, National Cancer Institute

Lisa Peterson, PhD, University of Minnesota

Michael Pino, DVM, PhD, Sanofi

Keith Soper, PhD, Merck Research Laboratories

Richard Miller, DVM, PhD, GlaxoSmithKline (BSC Liaison/non-voting
observer)

Charge to the Panel

- Review the scientific and technical elements of the study and its presentation
- Determine whether the study's experimental design, conduct, and findings support the NTP's conclusions

Levels of Evidence of Carcinogenic Activity

- **Clear evidence of carcinogenic activity**
 - Dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy
- **Some evidence of carcinogenic activity**
 - Chemical-related increased incidence of neoplasms in which the strength of the response is less than that required for clear evidence
- **Equivocal evidence of carcinogenic activity**
 - Marginal increase of neoplasms that may be chemical related
- **No evidence**
- **Inadequate study**

N,N-Dimethyl-*p*-toluidine

A high production chemical with potential for widespread human exposure due to its use in dental materials and bone cements

For the 2-year gavage study, the panel recommended accepting the conclusions as written (8-2-0)
Two panelists thought the hepatocellular carcinomas were the primary liver tumors in male rats

Sex/Species	Evidence	Neoplastic lesions
Male Rats	CE	Hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined); nasal cavity neoplasms (primarily nasal cavity transitional epithelium adenoma)
Female Rats	CE	Hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined)
Male Mice	CE	Hepatocellular adenoma (multiple), hepatocellular carcinoma, and hepatoblastoma
Female Mice	CE	Hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma; alveolar/bronchiolar neoplasms (primarily adenoma)

CE = clear evidence

Ginkgo biloba Extract

Herbal supplement

For the 2-year gavage study, the panel recommended accepting the conclusions as written (7 for, 1 against, 0 abstained, 2 recused)

One panelist thought the conclusion for the thyroid tumors in female rats should be changed from *some evidence* to *equivocal evidence*.

Sex/Species	Evidence	Neoplastic lesions
Male Rats	SE	Thyroid gland follicular cell adenoma
Female Rats	SE	Thyroid gland follicular cell neoplasms
Male Mice	CE	Hepatocellular carcinoma and hepatoblastoma
Female Mice	CE	Hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma

SE = some evidence; CE = clear evidence

β-Picoline

Used as a solvent, as a laboratory reagent, and intermediate in the manufacture of insecticides, waterproofing agents, niacin, and niacinamide

For the 2-year drinking water study, the panel recommended accepting the conclusions as written (10-0-0)

Sex/Species	Evidence	Neoplastic lesions
Male Rats	NE	–
Female Rats	SE	Alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined)
Male Mice	EE	Alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined)
Female Mice	CE	Alveolar/bronchiolar adenoma or carcinoma (combined); hepatocellular carcinoma and hepatoblastoma

NE = no evidence; SE = some evidence; EE = equivocal evidence; CE = clear evidence

Pyrogallol

Used as a dye, corrosion inhibitor and fine arts photographic developer

For the 2-year dermal study, the panel recommended accepting the conclusions as written (10-0-0)

Sex/Species	Evidence	Neoplastic lesions
Male Rats	NE	–
Female Rats	NE	–
Male Mice	EE	Squamous cell papilloma of the skin at the site of application
Female Mice	SE	Squamous cell carcinoma of the skin at the site of application

NE = no evidence; EE = equivocal evidence; SE = some evidence

Trimethylolpropane Triacrylate (TMPTA)

Multifunctional monomer with a wide range of industrial applications

For the 2-year dermal study, the panel recommended changing the conclusion for male rats from *some evidence* to *equivocal evidence* by an 8-2-0 vote. Two panelists felt the *some evidence* conclusion was more appropriate.

Upon further review, the NTP staff concurred with the panel's recommendation based on the variability of these tumors in the historical control database.

The panel recommended accepting the conclusions for female rats and male mice as written.

Sex/Species	Evidence	Neoplastic lesions
Male Rats	EE	Malignant mesothelioma
Female Rats	NE	–
Male Mice	NE	–
Female Mice	SE	Uncommon malignant hepatic neoplasms (hepatoblastoma and hepatocholangiocarcinoma) and stromal polyp or stromal sarcoma of the uterus

EE = equivocal evidence; NE = no evidence; SE = some evidence

Trimethylolpropane Triacrylate (TMPTA)

For female mice, the panel recommended accepting the overall conclusion of *some evidence of carcinogenic activity* but concluded that the occurrence of hepatoblastoma “may have been related” to TMPTA (i.e. *equivocal evidence*) by a 10-0-0 vote.

Upon further review, the NTP staff concluded that the incidences of hepatoblastoma were related to treatment and recommended that this tumor type be retained in the conclusion along with hepatocholangiocarcinoma as *some evidence of carcinogenic activity* of TMPTA in female mice.

Sex/Species	Evidence	Neoplastic lesions
Male Rats	EE	Malignant mesothelioma
Female Rats	NE	–
Male Mice	NE	–
Female Mice	SE	Uncommon malignant hepatic neoplasms (hepatoblastoma and hepatocholangiocarcinoma) and stromal polyp or stromal sarcoma of the uterus

EE = equivocal evidence; NE = no evidence; SE = some evidence

3' -Azido-3' -deoxythymidine (AZT)

Treatment and prevention of AIDS including mother-to-child transmission of HIV during pregnancy and labor

For the 45-week in *utero* and postnatal gavage study in heterozygous F1 p53+/- mice, the panel recommended accepting the conclusions as written (10-0-0)

Sex/Species	Evidence	Neoplastic lesions
Male p53+/- Mice	CE	Hepatocellular neoplasms (predominantly adenomas)
Female p53+/- Mice	EE	Malignant lymphoma

CE = clear evidence; EE = equivocal evidence

Mixtures of 3'-Azido-3'-deoxythymidine (AZT), Lamivudine (3TC) and Nevirapine (NVP)

Combination therapies for AIDS

For the 45-week in *utero* and postnatal gavage study in heterozygous F1 p53+/- mice, the panel recommended accepting the conclusions as written (10-0-0)

Therapeutics	Evidence	Male p53+/- Mice
AZT	CE	Hepatocellular adenoma
3TC	NE	—
NVP	NE	—
AZT + 3TC	CE	Hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined)
AZT + 3TC + NVP	CE	Hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined)

CE = clear evidence; NE = no evidence

Mixtures of 3'-Azido-3'-deoxythymidine (AZT), Lamivudine (3TC) and Nevirapine (NVP)

Combination therapies for AIDS

For the 45-week in *utero* and postnatal gavage study in heterozygous F1 p53+/- mice, the panel recommended accepting the conclusions as written (10-0-0)

Therapeutics	Evidence	Female p53+/- Mice
AZT	NE	–
3TC	EE	Mammary gland adenoacanthoma or adenocarcinoma (combined)
NVP	EE	Malignant lymphoma
AZT + 3TC	EE	Malignant lymphoma
AZT + 3TC + NVP	EE	Malignant lymphoma

NE = no evidence; EE = equivocal evidence

Next steps

- All NTP staff recommendations are still under consideration by the NTP Associate Director and Director, who will make the final decisions.